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(54) **Substance P antagonists for the treatment of emesis**

Substanz P Antagonisten zur Behandlung von Erbrechen

Antagonistes de la substance P pour le traitement du vomissement

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(56) References cited:

EP-A- 0 533 280
EP-A- 0 615 751
WO-A-92/17449
WO-A-92/20676
WO-A-92/21677
WO-A-93/00330
WO-A-93/00331
WO-A-93/06099
WO-A-93/10073
WO-A-93/19064
WO-A-93/23380
WO-A-94/13663
WO-A-94/20500

- **EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 249, page R3 C. BOUNTRA ET AL. 'ANTI-EMETIC PROFILE OF A NON-PEPTIDE NEUROKININ NK1 RECEPTOR ANTAGONIST, CP-99994, IN FERRETS'**
- **EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 250, page R5 F.D. TATTERSALL ET AL. 'THE TACHYKININ NK1 RECEPTOR ANTAGONIST CP-99994 ATTENUATES CISPLATIN INDUCED EMESIS IN THE FERRET'**

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

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Des ription

[0001] The present invention relates to the use of certain compounds for the manufacture of medicament for the treatment or prevention of emesis in mammals, including humans. The pharmaceutically active compounds employed in this invention are substance P receptor antagonists.

[0002] The following references refer, collectively, to quinuclidine, piperidine, and azanorbornane derivatives and related compounds that exhibit activity as substance P receptor antagonists: United States Patent 5,162,339, which issued on November 11, 1992; United States Patent Application 724,268, filed July 1, 1991; PCT Patent Application PCT/US 91/02853, filed April 25, 1991; PCT Patent Application PCT/US 91/03369, filed May 14, 1991; PCT Patent Application PCT/US 91/05776, filed August 20, 1991; PCT Patent Application PCT/US 92/00113, filed January 17, 1992; PCT Patent Application PCT/US 92/03571, filed May 5, 1992 corresponding to WO93/00331; PCT Patent Application PCT/US 92/03317, filed April 28, 1992; PCT Patent Application PCT/US 92/04697, filed June 11, 1992; United States Patent Application 766,488, filed September 26, 1991; United States Patent Application 790,934, filed November 12, 1991; PCT Patent Application PCT/US 92/04002, filed May 19, 1992; Japanese Patent Application 065337/92, filed March 23, 1992; United States Patent Application 932,392, filed August 19, 1992; and United States Patent Application 988,653, filed December 10, 1992; WO 90/05729 ; WO92/21677; and United States Patent Application 026328, filed March 4, 1993.

[0003] European Patent Application 533280A1, published March 24, 1993 refers to the use of substance P antagonists in the treatment of emesis.

[0004] The present invention relates to the use of a compound for the manufacture of a medicament for the treatment or prevention of emesis in a mammal, where the compound is selected from the following group, or is a pharmaceutically acceptable salt thereof:

(2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl) amino-2-phenylpiperidine;
(2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo [2.2.2] octan-3-ainine; and
(2S, 3S)-N-(5-tert-butyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine.

[0005] The treatment of emesis includes the treatment of nausea, retching and vomiting. Emesis includes acute emesis, delayed emesis and anticipatory emesis. The substance P receptor antagonists of this invention are useful in the treatment of emesis, however induced. For example, emesis may be induced by drugs such as cancer chemotherapeutic agents (e.g., cyclophosphamide, carmustine, lomustine and chlorambucil), cytotoxic antibiotics (e.g., dactinomycin, doxorubicin, mitomycin-C and bl omycin), opioid analgesics (e.g., morphine), anti-metabolites (e.g., cytarabine, methotrexate and 5-fluorouracil), vinca alkaloids (e.g., etoposide, vinblastine and vincristine), and other drugs such as cisplatin, dacarbazine, procarbazine and hydroxyurea. Emesis may also be induced by radiation sickness, radiation therapy, poisons, toxins such as those caused by metabolic disorders or by infection (e.g., gastritis), pregnancy, vestibular disorders such as motion sickness, post-operative sickness, gastrointestinal obstruction, reduced gastrointestinal motility, visceral pain (e.g., myocardial infarction or peritonitis), migraine, increased intercranial pressure or decreased intercranial pressure (e.g., altitude sickness).

[0006] The compounds of this invention may also be used to treat or prevent emesis induced by the drug ipecac.

[0007] A compound used in the present invention may be prepared as described in PCT Patent Application PCT/US 92/03571 corresponding to WO93/00331, which designates the United States and was filed in the United States Receiving Office on May 5, 1992. Other compound used in the present invention are described in WO90/05729 and WO92/21677.

[0008] The compounds used in the present invention (hereinafter referred to, collectively, as the "therapeutic agents") and the pharmaceutically acceptable salts thereof are useful as substance P receptor antagonists, i.e., they possess the ability to antagonize the effects of tachykinins at the substance P receptor site in mammals, and therefore they are able to function as therapeutic agents in the treatment and prevention of emesis in an afflicted mammal.

[0009] The therapeutic agents are basic in nature and are capable of forming a wide variety of different salts with various inorganic and organic acids. Examples of acids that form suitable pharmaceutically acceptable salts for use in this invention are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

[0010] Although such salts must be pharmaceutically acceptable for administration to mammals, it is often desirable in practice to initially isolate a therapeutic agent from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base therapeutic agents of this invention are readily prepared by treating the base com-

pound with a substantially equivalent amount of the chosen mineral or organic acid in an aqu ous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained.

[0011] Th th rap utic agents and their pharmaceutically acceptable salts exhibit substance P receptor-binding activity and therefore are of value in the treatment and prevention of emesis in mammals, including humans.

[0012] The therapeutic agents and the pharmaceutically acceptable salts thereof can be administered via either the oral, topical, rectal or parenteral routes. In general, these compounds are most desirably administered in dosages ranging from 5.0 mg up to 1500 mg per day, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of 0.07 mg to 21 mg per kg of body weight per day is most desirably employed. Variations may nevertheless occur depending upon the species of animal being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

[0013] The therapeutic agents and their pharmaceutically acceptable salts may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the therapeutic agents of this invention can be administered in a wide variety of different dosage forms, i.e., they- may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, suppositories, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutic compounds of this invention are present in such dosage forms at concentration levels ranging from 5.0% to 70% by weight.

[0014] For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), .alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also b employ d as fillers in gelatin capsules; pr - ferred materials in this connection also include lactose or milk sugar as well as high molecular w ight poly thylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

[0015] For parenteral administration, solutions of a therapeutic agent in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be -suitably buffered if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

[0016] The activity of the therapeutic agents as substance P receptor antagonists may be determined by their ability to inhibit the binding of substance P at its receptor sites in bovine caudate tissue, employing radioactive ligands to visualize the tachykinin receptors by means of autoradiography. The substance P antagonizing activity of the herein described compounds may be evaluated by using the standard assay procedure described by M. A. Cascieri et al., as reported in the Journal of Biological Chemistry, Vol. 258, p. 5158 (1983). This method essentially involves determining the concentration of the individual compound required to reduce by 50% the amount of radiolabelled substance P ligands at their receptor sites in said isolated cow tissues, thereby affording characteristic IC_{50} values for each compound tested.

[0017] In this procedure, bovine caudate tissue is removed from a -70°C freezer and homogenized in 50 -volumes (w./v.) of an ice-cold 50 mM Tris (i.e., trimethamine which is 2-amino-2-hydroxymethyl-1,3-propanediol) hydrochloride buffer having a pH of 7.7. The homogenate is centrifuged at 30,000 x G for a period of 20 minutes. The pellet is resuspended in 50 volumes of Tris buffer, rehomogenized and then recentrifuged at 30,000 x G for another twenty- minute period. The pellet is then resuspended in 40 volumes of ice-cold 50 mM Tris buffer (pH 7.7) containing 2 mM of calcium chloride, 2 mM of magnesium chloride, 4 µg/ml of bacitracin, 4µg/ml of leupeptin, 2µg of chymostatin and 200 g/ml of bovine serum albumin. This step completes the production of the tissue preparation.

[0018] The radioligand binding procedure is then carried out in the following manner, viz., by initiating the reaction via the addition of 100 µl of the test compound

made up to a concentration of 1 µM, followed by the addition of 100 µl of radioactive ligand made up to a final concentration 0.5 mM and then finally by the addition of 800 µl of the tissue pr paration produced as described above. The final volume is thus 1.0 ml, and the reaction mixture is next vortexed and incubated at room temperature (ca. 20°C) for a period of 20 minutes. The tubes are then filtered using a cell harvester, and the glass fiber filters (Whatman GF/B) are washed four times with 50 mM of Tris buffer (pH. 7.7), with the filters having previously been presoaked for a period of two hours prior to the filtering procedure. Radioactivity is then determined in a Beta counter at 53% counting efficiency, and the IC_{50} values are calculated by using standard statistical methods.

[0019] The ability of the therapeutic agents to inhibit substance P induced effects in vivo may be determined by the following procedures "a" through "c". (Procedures "a" through "c" are described in Nagahisa et al., European Journal of Pharmacology, 217, 191-5 (1992), which is incorporated herein by reference in its entirety.)

a. Plasma extravasation in the skin

[0020] Plasma extravasation is induced by intradermal administration of substance P (50 µl, 0.01% BSA-saline solution) in dorsal skin of pentobarbital (25 mg/kg i.p.) anesthetized male Hartley guinea pigs weighing 450-500 g. The compound to be tested is dissolved in 0.1% methyl cellulose-water (MC) and dosed p.o. 1 hour before substance P challenge (3 pmol/site). Evans blue dye (30 mg/kg) is administered intravenously 5 minutes before challenge. After 10 minutes, the animals are sacrificed, the dorsal skin is removed, and the blue spots are punched out using a cork borer (11.5 mm oral dose (o.d.)). Tissue dye content is quantitated after overnight formamide extraction at 600 nm absorbance.

b. Capsaicin-induced plasma extravasation

[0021] Plasma extravasation is induced by intraperitoneal injection of capsaicin (10 ml of 30 µM solution in 0.1% BSA/saline) into pentobarbital anesthetized (25 mg/kg i.p.) guinea pigs. The compound to be tested is dissolved in 0.1% MC and dosed p.o. 1 hour before capsaicin challenge. Evans blue dye (30 mg/kg) is administered i.v. 5 minutes before challenge. After 10 minutes, the animals are sacrificed, and both right and left ureters are removed. Tissue dye content is quantitated as in "a" above.

c. Acetic acid-induced abdominal stretching

[0022] Male ddY mice (SLC, Japan), weighing 14-18 g, were fasted overnight. The compound to be tested is dissolved in 0.1% MC and dosed p.o. 0.5 hour before acetic acid (AA) inj ction (0.7%, 0.16 ml/10 g body weight). The animals are placed in clear beakers (1 per beaker) and the stretching response is counted 10 to 20 minutes after the AA injection (10 minut interval).

[0023] The anti-emetic activity of compounds that are substance P receptor antagonists may be determined by evaluating their ability to reduce the p rcentage of ferrets exhibiting emesis in response to cisplatinum exposure (10 mg/kg, i.p.). The compound (2S, 3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine inhibited cisplatinum induced emesis in ferrets when administered at a dose of 1 mg/kg s.c. (subcutaneously), 30 minutes before cisplatinum exposure. The compound (2S,3S)-3-(2-methoxy-5-trifluoromethyoxybenzyl)amino-2-phenylpiperidine inhibited cisplatinum induced emesis in ferrets when administered at a dose of 1 mg/kg s.c., 30 minutes before cisplatinum exposure.

Claims

1. The use of a compound for the manufacture of a medicament for the treatment or prevention of emesis in a mammal, including a human, where the compound is selected from the group consisting of (2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl) amino-2-phenylpiperidine, (2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine and (2S,3S)-N-(5-tert-butyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine: or is a pharmaceutically acceptable salt thereof.

2. The use of a compound according to claim 1 where the compound is (2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine or a pharmaceutically acceptable salt thereof.

3. The use of a compound according to claim 1 where the compound is (2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo [2.2.2]octan-3-amine or a pharmaceutically acceptable salt thereof.

4. The use of a compound according to claim 1 where the compound is (2S,3S)-N-(5-tert-butyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo [2.2.2]octan-3-amine or a pharmaceutically acceptable salt thereof.

Patentansprüche

1. Verwendung einer Verbindung zur Herstellung eines Arzneimittels zur Behandlung oder Verhinderung von Emesis bei einem Säuger, einschließlich eines Menschen, wobei die Verbindung aus der Gruppe, bestehend aus (2S,3S)-3-(2-Methoxy-5-trifluormethoxybenzyl)amino-2-phenylpiperidin,

(2S,3S)-N-(5-Isopropyl-2-methoxyph nyl)m thyl-2-diph nylmethyl-1-azabicyclo[2.2.2]octan-3-amin und (2S,3S)-N-(5-tert-Butyl-2-methoxyphenyl)m - thyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amin ausgewählt ist oder ein pharmazeutisch verträgliches Salz davon ist.

2. Verwendung einer Verbindung nach Anspruch 1, wobei die Verbindung (2S,3S)-3-(2-Methoxy-5-trifluormethoxybenzyl)amino-2-phenylpiperidin oder ein pharmazeutisch verträgliches Salz davon ist.

3. Verwendung einer Verbindung nach Anspruch 1, wobei die Verbindung (2S,3S)-N-(5-Isopropyl-2-methoxyphenyl) methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amin oder ein pharmazeutisch verträgliches Salz davon ist.

4. Verwendung einer Verbindung nach Anspruch 1, wobei die Verbindung (2S,3S)-N-(5-tert-Butyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amin oder ein pharmazeutisch verträgliches Salz davon ist.

Revendications

1. Utilisation d'un composé pour la production d'un médicament destiné au traitement ou à la prévention des vomissements chez un mammifère, y compris l'homme, dans laquelle le composé est choisi dans le groupe consistant en la (2S,3S)-3-(2-méthoxy-5-trifluorométhoxybenzyl)amino-2-phénylpipéridine, la (2S,3S)-N-(5-isopropyl-2-méthoxyphényl)méthyl-2-diphénylméthyl-1-azabicyclo[2.2.2] octane-3-amine et la (2S,3S)-N-5-(tertio-butyl-2-méthoxyphényl)méthyl-2-diphénylméthyl-1-azabicyclo[2.2.2]octane-3-amine ou consiste en un de leurs sels pharmaceutiquement acceptables.

2. Utilisation d'un composé suivant la revendication 1, dans laquelle le composé est la (2S,3S)-3-(2-méthoxy-5-trifluorométhoxybenzyl)amino-2-phénylpipéridine ou un de ses sels pharmaceutiquement acceptables.

3. Utilisation d'un composé suivant la revendication 1, dans laquelle le composé est la (2S,3S)-N-(5-isopropyl-2-méthoxyphényl)méthyl-2-diphénylméthyl-1-azabicyclo-[2.2.2]octane-3-amine ou un de ses sels pharmaceutiquement acceptables.

4. Utilisation d'un composé suivant la revendication 1, dans laquelle le composé est la (2S,3S)-N-(5-tertiobutyl-2-méthoxyphényl)méthyl-2-diphénylméthyl-1-azabicyclo-[2.2.2]octan-3-amine ou un de ses sels pharmaceutiquement acceptables.